which are the longer lesion patients, the ones that real need it as a bail out, and maybe that is something you could use to get the thing approved.

DR. LASKEY: At risk of being redundant, I share everyone's comments to date. We appreciate the effect that went into this. We appreciate your energy in hanging with it, in what was clearly an avalanche of reticence on the panel's part. I think that there is a need for a device that you can reach for when you are in trouble, and I wonder out loud whether it is possible to construct a reasonably statistically meaningful registry of abrupt and threatened closure to make your case a little stronger.

But backing into it this way, backing off from a study which did not have its desired endpoint reached because of reticence on the part of investigators and so forth, and then again doing a post hoc retrospective look at a different definition I think all conspired against you. But it is important to proceed here and give clinicians a useful bail-out device, and I would think that a properly conducted registry with a good look, a very stringent look at threatened closure may help the cause.

DR. FREISCHLAG: Mu concern is I am not sure PTA or stents are any better than the natural history of the disease, and to convince me that this isn't hurting people longer data is needed to know that at two, three and four years if these things go down, they don't get worse. I know as a surgeon, when I do a fem/pop and it goes down a lot of my patients get worse when the bypass goes down because of the lack of collaterals. And, I am really concerned that nine months in my mind isn't long. These patients do live about five years and I think we need to look at them in a long-term piece and probably have a different analysis to convince me that they will be okay in the long term.

DR. DEWEESE: I believe the original motion was that with the information we had today that I should vote, and for that reason I voted that we not approve but I would have accepted a motion that said approved with if they had given us all the information we asked for today. But I said what I said.

DR. ROBERTS: I guess the only thing that I would say is that I really congratulate the sponsors on sticking with this trial, and I

understand how difficult this is. I would also say to the investigators that it is so sad that you decided not to do the patients that really needed to be done because I think if you had done the really difficult lesions you probably would have found that, in fact, the stents might have worked and would have shown a benefit. And, I would be very hopeful and encouraging for that data, if it exists, to be brought back, wherever it comes from, and used as data to help support the fact that in lesions that perhaps were not the lesions that were studied in this group, which were the very short lesions, the lesions that PTA is going to do okay with instead of studying the tough ones which might have shown a benefit, and that is unfortunate.

DR. TRACY: Mr. Jarvis, did you have any comments that you would like to make?

MR. JARVIS: No.

DR. TRACY: Then, I think that ends this portion of the meeting and I also would like to thank the sponsor and applaud their effects for putting together this very, very difficult trial, and wish you luck in your future endeavors with this.

We are going to shift gears a little bit

here and be discussing at this point clinical study design issues for iliac stenting. You might want to wiggle in your chair a little bit but I think we will keep pressing on here and I will call this to order and invite the FDA presentation.

Clinical Study Design Issues for Iliac Stenting

MS. DANIELSON: We have some really important questions here and, in light of what we have just seen, the difficulty of doing randomized trials when we have rampant off-label use of stents, I am going to limit some of the slides and questions that I am going through here.

[Slide]

One of the things that I want to emphasize is that right now there are only two stents approved for the iliac artery, and they are both for suboptimal angioplasty. The first stent was approved in '91 and the second stent was approved in '96.

Currently, ongoing studies are randomized trials and they are proceeding very slowly. Some of the limitations of these trials for why they are proceeding so slowly appear to be that they are randomized; they are using the currently approved stents that are approved for iliac arteries as the

controls and there are limitations with these stents and the availability of other stents for off-label use.

[Slide]

The first question is, given our current understanding of stenting the iliac artery following suboptimal angioplasty, please discuss the need for a randomized control trial to evaluate a new iliac stent system for a suboptimal indication.

[Slide]

I am going to go right to question four. This addresses the primary stent for the iliac artery. Given our current understanding of stenting in iliac arteries over the past ten years, please discuss the following points regarding the trial design for a primary stent indication: Is a randomized trial necessary? What are the appropriate controls? Should a primary stent trial require a superiority-based hypothesis? Is an equivalence hypothesis acceptable? And, what are the appropriate endpoints? And, any additional comments would be appreciated by FDA. Thank you.

DR. TRACY: All right. We are going to, at this point, allow the open public hearing. I

know there are a number of people who are waiting to make some presentations this afternoon.

Open Public Hearing

MS. MOYNAHAN: We will have Chris White, and if you could just state for the record any conflict of interest issues, including whether your travel was paid for, or whether you are an investigator in an iliac trial.

DR. WHITE: My name is Chris White. I am a clinical cardiologist at the Ochsner Clinic, in New Orleans. My travel is, hopefully, going to be paid for by the ACC, the American College of Cardiology, but that has not been settled. I am here with that expectation.

[Laughter]

I should say that today I was asked to come by Dr. Rosenfield, who is the Chairman of the Peripheral Vascular Disease Committee of the ACC, because I have a large practice in peripheral vascular intervention. It makes up about a third of our practice. There is a group of four of us who do about 3000 interventions a year, and about one third of that is peripheral. We are involved in many of the current clinical trials, both in coronary and peripheral, and are very familiar with

the difficulties that the panel faces and we face as clinicians waiting for devices to come to us.

[Slide]

I am actually going to propose some radical issues today. Some I feel are true; some maybe we will just try to be provocative about.

[Slide]

The first issue I wanted to raise, and I heard this actually this morning, is that the terminology is really difficult, and I think Dr. Laskey actually mentioned this. It gets very confusing in the peripheral vasculature trying to understand what the indications are and what we are talking about.

I would propose that we talk about primary stent placement and provisional stent placement. The term suboptimal has been used a lot this morning but the trouble with suboptimal is that it is very subjective. Primary stent placement means that you are going to end up with a stent regardless of what the result with pre-dilatation or preparation of the artery is, and I think that is a special category of patients. In fact, it may be a surprise to you to know that about 90 percent of all the peripheral interventions that are

performed in the country today -- maybe more than 90 percent -- are done in this category, that is, primary stent placement. We may do them under the umbrella of provisional but everybody intends to finish with a stent. So, primary stent placement is the way we practice. It has been responsible for the explosion of the clinical procedures that are being done.

Provisional stent placement is maybe more cost effective and maybe more attractive. That is, can you get away with balloon dilatation alone? In one category of patients can we use balloon angioplasty alone? And, in one setting should the stent be used to support balloon angioplasty?

You heard this morning a trial based, or at least some data based around suboptimal stent placement. It would also go toward unfavorable anatomies. For example, typically a long, totally occluded iliac lesion would not even be a candidate for balloon angioplasty. So, you would be planning to use provisional stenting for that lesion from the git-go.

[Slide]

One of the radical concepts I would like to propose is that you would consider stents only

in two categories. You would consider stents in a coronary category and non-coronary category. I believe that it is reasonably difficult to conceive approval of stents for every named vessel in the body, and that we would have a debate about a vascular device salvaging an interventional procedure in the SFA with a popliteal or renal or subclavian or brachial or an axillary. Really, if you insist on doing that, then what you insist on doing is making most of us practice in the current manner, which is off-label use.

I believe that we can talk about specifics of target vessel issues, and certainly renal is different than a leg; brain is different than the kidney. But, I do believe that we are talking about ischemia to an end organ and we are talking, particularly in the suboptimal indication or the provisional indication, about salvaging a balloon angioplasty. So, if the indication for balloon angioplasty is met which is not what we are approving, we are approving the stent, and balloon angioplasty is insufficient for whatever reason, then a stent to support that indication really goes past the end organ in which the stent is being used.

I would support that argument by listing for you the number of coronary applications that I use approved stents for, but no one would ever consider a trial for a bifurcation lesion, for example. We do not have specifically approved stents for total occlusions, for bifurcations, for vein grafts. The list is endless where we put approved stents once we have an idea. And, I think that non-coronary applications would lend themselves to this, although it really goes against the current stream of thinking.

The second thing is that it would bring some consistency to this field of terrible inconsistency, and that is that stents, balloons, filter devices, other peripheral devices could all be considered in the same way. Sponsors and physicians alike could have some idea of what the ground rules were for coming to some idea of acceptability.

[Slide]

As I mentioned to you, I think it is not possible to approve for every named vessel. We talked about the indications. I think that we could approve these devices for non-coronary use and it would be at the physician's discretion to

use these stents in a non-coronary bed for the approved indication. What I mean is that if I am going to use this stent as a bail out or as a suboptimal or as a provisional stent, that would be my decision to use that stent in the popliteal or the iliac or the renal, but you would decide whether this was a reasonable stent for a bail out indication, not specifically the artery for which it was approved. Of course, you could approve it and you could say I like this stent for everything but ... and you could list limitations.

I can tell you that there is going to be a day when there will be approved carotic stents, and some of those stents are going to be very nice for use in other parts of the body. So, you will have an approved carotid stent that I will use as an off-label maybe below the knee, maybe in the popliteal. So, the point would be you could decide that you don't think this stent does very well in any end organ and you could approve it with those limitations.

[Slide]

I think it is difficult to do randomized trials. You have all heard that this morning. When the control group is clinically unattractive,

even though the science is excellent, the trial won't get done. I cannot randomize patients to a clinically unattractive subgroup.

The other problem is that when the unapproved devices -- I shouldn't say unapproved, when the approved but off-label devices are superior to the currently approved devices it is very difficult to randomize to the old technology and put my patient at some disadvantage or some risk.

I think that randomization is still suitable for primary stenting indications, and that was the purpose of the original trial this morning. That is, if I am going to put a stent in for a long-term patency indication, I do believe that randomization is appropriate.

[Slide]

When we look at non-randomized trials, the literature supports a very high success rate and low complication rate for iliac procedures. I think we have a long ten-year history of these devices and we can look at what is acceptable.

I think registry data and data with performance objectives offer the opportunity to look at real-world data versus the artificial world

of randomized trials. We pride ourselves on some randomized trials and, yet, our patient population does not fit the randomized trial data. Registry data allows us to put these devices into regular patients that we see every day and to look and collect that meaningful data about real-world use.

Of course, we have a good amount of historical control data in many of these subsets in order to create meaningful objective criteria. Again, I believe that non-randomized trials are more suitable for the provisional stent indication.

[Slide]

The endpoints for provisional stent placement I would suggest would be procedural safety and efficacy, to be defined by the sponsor and the committee. Thirty-day safety and efficacy numbers should be collected in the provisional stent placement category, but I would not insist on any longer formal follow-up than 30 days when we talk about salvaging a failed angioplasty because I think we make no commitment in that trial to provide an enhanced long-term outcome. We are simply saving the day and we should evaluate the device for that purpose.

On the other hand, I would like to make

sure, just as I believe one of the panel members suggested today, that bad things don't happen at late follow-up. So, I believe that postmarket surveillance should be seriously used at some late date to look at repeat procedures and limb salvage, particularly for the iliacs, and that primary stent placement would also include at least six-month follow-up -- duplex, ultrasound ankle brachial index. I don't believe there is a big tail-off in stent patency after six months and I think that would be a reasonable time.

[Slide]

I think that primary stent trials are difficult. There is currently no approved stent, yet it is the most commonly performed procedure in iliacs today. We don't really have anything to compare. It is not possible to do a head-to-head trial because the only approved stents are for suboptimal or provisional stenting. So, it really isn't possible to do a primary stent implantation in the iliacs as a head-to-head trial until we get an approved stent for that indication. I think patency at six months is adequate. I would look at safety at 30 days, and I would be serious about postmarket surveillance for late complications.

Again, I think it might be appropriate to randomize primary with an experimental stent for provisional indications for the approved stent. That would be I think appropriate.

[Slide]

I think it is very important that the committee keep in mind fast-track approvals for life-saving devices. It sometimes is very difficult to get devices through the system that have a small market value but which would save lives. I am specifically talking about things like covered stents in the iliacs for big tears and retroperitoneal bleeding. These devices should be accelerated and pushed through the approval process to get them into clinicians' hands.

[Slide]

I think the committee ought to consider seriously surrogate endpoints, particularly for distal embolization devices. I think it is a good thing to prevent distal emboli, and I think that efficacy ought to be equivalent to debris retrieval. Distal embolization is clearly harmful. It is just a matter of degree how harmful it is. And, I would believe that registry data with objective performance criteria would suffice for

adequacy as opposed to a huge trial demanding some clinical endpoint improvement.

That is all I have. Thank you for your attention.

DR. ANSEL: I am Gary Ansel again, and the disclosures are the same as before.

I am going to make this nice and brief, with no slides. One of the things that does come up a lot on committee discussions about using angioplasty and stents and things is long-term patency. Oftentimes there is mention of surgical patency versus stenting patency. What I guess I want to bring to your attention is that these are two vastly different procedures. With the downsizing of these percutaneous procedures, the closure devices that are now available, as you can see the complication rates of these outpatient procedures are extremely low.

I think that assisted patency, whether it be two or three procedures, at two to three years is what we should be looking at in concert with the patient's complications -- their survivability, their functionability and whether or not they are in a nursing home or independent living.

That is all I am going to bring up. Thank

you.

DR. ROSENFIELD: I want to thank Chris for coming up today. It is a long haul from New Orleans. He is really respected within the vascular community in general. That applies to surgery, radiology, cardiology -- people that perform vascular interventions.

I also just want to make an aside comment about this morning. I think the panel also deserves a lot of credit for getting this huge sum of data and having to process that and figure out whether a device should be approved or not. That is going to be a huge task, I guess.

I guess the first thing to say is that I wrote up a letter to Dr. Doug Zipes, who is the current president of the American College of Cardiology. And, as the Chairman of the Peripheral Vascular Disease Committee, I took it upon myself, having met Megan about three weeks ago and realizing that this open session was going to occur, I took advantage of that and asked my colleagues to come and help offer some of our own thoughts. So, I appreciate the panel's receptiveness to those thoughts.

In that spirit, I put together a letter

that I wrote to Dr. Zipes that I thought summarized some of our feelings about these issues which are very difficult for us as clinicians and you as a panel to have to wrestle with. Chris, I think, summarized what the content of my letter is very nicely. That has been distributed to all the panel members. No? It didn't get around.

MS. MOYNAHAN: It wasn't collated, but it went to the most important people, which are the transcriptionist and the summary writer. It will make it into the record.

DR. ROSENFIELD: Well, I could take this time to read this. I am not sure that you want that, but it might be better to more effectively distribute it to the panel members for their post hoc review. It is up to you.

MS. MOYNAHAN: Do you want to touch on just some of the most important points while we finish collating that?

DR. ROSENFIELD: Sure, if you will bear with me because I didn't put slides together. With all that has gone on over the past 24 hours I didn't actually have a chance.

The intent was to answer some of your specific questions about iliac stents. Just to

focus in on the iliac stenoses, I too share Dr. Laskey's concern about sort of rampant, widespread stenting for every and any indication regardless of whether there is any appropriate data to support that. So, everything that I say is taken in that light.

On the other hand, I think that there has been a tremendous change over the past five years where clinicians that are in practice realize that stenting really has very little downside, and the potential of a failed balloon angioplasty, whether it is acute or subacute, has a huge downside.

We would be concerned if we had problems within stents. If there was a high rate of infection -- I think that was one of the biggest concerns early on, or if there is a high rate of thrombosis of stents in any given venue. It turns out that that is not the case. So, to me, as a clinician who is in practice. I am trying to do the best thing for my patient.

Then the question comes up is it possible to randomize patients between primary stenting versus balloon angioplasty when you are faced with a patient who has what you think is a suboptimal result and you think in your heart of hears that

this my father or my mother on the table, would I leave this result alone? And, you say to yourself no, I wouldn't. Do I have a stent available? Yes, I do. Okay, then you go ahead and you put the stent in.

Now, that doesn't happen to every patient, and I don't think that the impression should be given to this panel that that happens to every patient, but it does present a real problem for clinicians. Actually, Dr. Zipes made the commentary in his response to me, which is attached, that the situation was similar with RF oblation where there was a difficulty in doing randomized controlled trials because we had a technology and it didn't make sense to randomize those patients because the technology was so much better that you didn't want to compromise your own individual patient's position.

So, do I think that randomized controlled trials are appropriate and necessary for getting approval for stents in iliac stenoses? No, I would say that I would divide this up, like Chris did, into provisional stenting. I think there should be the ability to get an approval for provisional stenting, that is, for a suboptimal result of

balloon angioplasty, however you might define that, and that that approval should be able to be based on historical controls. I think it is possible. It is not easy to come up with those historical controls and to develop a set of OPCs, but I think that that is the hard work that should probably be done because those of us who are now faced with these trials, as Ms. Danielson outlined, are faced with trying to enroll patients in trials -- we are faced with randomizing them to an outdated stent, an outdated technology with probably not as good results in the long term or even in the short term; probably not as safe a profile as the current stents against which we are randomizing them to.

So, the bottom line is that I think that it is probably not reasonable to ask industry to then ask clinicians to randomize the newer stent technology against outdated technology. There are only two stents approved for use in iliac arteries, and those were approved many, many years ago. There is a huge revolution in technology that makes the current devices much more favorable.

That was a long-winded answer. So, my position would be that I don't think we have to randomize against older technology. I think we

should be able to perform registries of newer stents for the provisional indication and develop a set of OPCs that would be acceptable for that.

Now, what about primary stenting as opposed to provisional stenting? I think that, on the other hand, deserves a longer term trial to demonstrate efficacy as opposed to the case of provisional stenting. I have expounded upon that in the letter that I wrote here.

What about iliac occlusions? I think that the practice of primary stenting for iliac occlusions is a widespread practice. It is probably a rare event that the iliac occlusion that is revascularized with balloon alone doesn't have a 5 mm residual gradient or a residual 50 percent stenosis. In other words, most of those patients already qualify for the suboptimal balloon result based on the previously approved stents -- WallStent and Palmaz stent. So, more than 95 percent of revascularized iliac occlusions will already satisfy those criteria. So, I don't believe it is appropriate to randomize those patients against balloon angioplasty alone. I think that is doing our patients a disservice.

So, given the fact that the safety profile

of placing these metallic structures in the iliac artery is pretty high, that is not really in question. The real question is what is the complication rate in terms of distal embolization and can you get a good acute result in those patients given that there is already a suboptimal outcome by definition? So, I would not support a position where you need to look at these patients in quite so long term a fashion because you are already talking about, in a majority of these patients, a suboptimal result.

So, you might say, well, why not compare them to surgery as another endpoint? These patients could have an aortal-femoral bypass. That is really the thing against which maybe you should compare them. I agree with Dr. Ansel that there is a real huge difference in the surgical approach. One is a major intervention and the other is not as major an intervention. One is easily retreated for restenotic lesions; the other is a much more difficult thing to retreat. And, the performance of the balloon angioplasty and stenting doesn't necessarily preclude the opportunity to intervene surgically at a later date. So, what are we losing by allowing a strategy of primary stenting in iliac

occlusions? I don't think much as long as the safety profile is good.

So, what I would argue for is looking very closely at safety endpoints and acute patency endpoints, say at 30 days in the case of iliac occlusions. I mean, I think this is something that should be open for discussion amongst clinicians and FDA and others that are involved in treating these patients, and industry who faces the real problem of how to get devices to market which we think are much better than the current devices that are out there and that the clinicians are clamoring for and patients are clamoring for. But we have this huge hurdle that we have to surmount and it is a real problem that I think should be open for discussion and resolution. Thank you.

DR. LASKEY: I just have one question for Ken. When we are talking about iliac, are we talking about iliac or are we going into iliofemoral, popliteal? What specifically are you referring to? Because in my mind, I didn't think there was an issue iliac.

DR. ROSENFIELD: Actually, the questions that the FDA asked were specifically related to iliac. Chris proposed this notion that you approve

stents for non-coronary and coronary applications, and I think what I outlined in my letter is a little bit different from that and it acknowledges that each vascular bed -- certain vascular beds you can sort of subset them and they have their own particular issues. Dr. DeWeese and I sort of met in the corridor this morning and talked a little bit about the issue of compression and the adductor canal and the specific issues that one has to deal with in the femoropopliteal access, and I think that is a special area that you need to sort of segregate out a little. So, I will disagree a little bit with Dr. White's comments in that regard.

On the other hand, I agree with him insofar as how are you going to get a stent approved for subclavian stenoses? I mean, I can tell you that subclavians do much better with stenting but you are never going to accumulate a trial of 200 or 300 subclavian patients randomized to balloon versus stenting. You are just never going to get there. So, does that mean we should never have a stent that is approved for the use in the subclavian arteries? No, I don't think it does. Subclavian is pretty much like the iliac in

terms of the bed it serves, although you do have the vertebrals so you have issues of safety that have to be addressed. You have to make sure that you are not going to embolize to the vertebral. But, aside from that, as long as you can get the job done safely and you create a nice hemodynamic result, those stents really fall in the same category as the iliac. So, I would be in favor of a registry for subclavian approval based on the performance we know of these same stents to be in the iliac arteries.

Now, carotids I think are a different situation. It is a little bit dependent on the blood that you are serving, and the cerebral vascular bed is special in its own right for a lot of reasons, and there are randomized trials already defined to address that.

The renal vascular bed I also think is a little bit of a unique bed. So, I would segregate things in that way, sort of femoropopliteal, aorta-iliac -- that is another one, the aorta. You are never going to find enough patients to stent the distal abdominal aorta in a randomized controlled fashion to be able to gain an indication for that. But do I think that stenting of the distal

abdominal aorta is better than balloon angioplasty alone? Absolutely. I wouldn't do it without it. I don't know if that answers your question, Dr. Laskey.

MR. DILLARD: I might just make a comment on this based on Dr. Rosenfield's comments. I am not sure, based on that last thing that you just said whether you are now a lumper or a splitter, but I will leave that maybe for a minute.

The main reason I think we wanted to focus on iliac here, even though this morning and afternoon was certainly dedicated to a little bit different discussion, is that that is predominantly where we have seen most of the clinical trials that have been focused on this particular area of the anatomy. It seems to be where we have the most investigations, not that it is the only place, and it is the one where we have real live issues with sponsors right now, their trial designs and their enrollment. And, if part of our job at the agency is to try to help stimulate doing clinical trials and trying to move them to fruition, this is an area that is particularly problematic, not that some of the others are not.

Further, and this is the last comment I

will make, is go ahead and focus today on iliac but it is probably not the last time we will talk about this particular area of vasculature and clinical trial designs. I am sure potentially we could get to the point where we could have a much broader discussion about a broad array of vascular beds and how that might affect stenting and particular trial designs. So, I appreciate your comments very much.

DR. ROSENFIELD: Can I just respond to that? What I was trying to get at is that I am a partial lumper but I am also a partial splitter. I don't know what the answer to this is, but I think that it requires a discussion of enlightened participants, panel members who are clinicians as well and very savvy as to the issues here, and clinicians such as Chris White and prominent folks like that, Gary Ansel, and then you folks and industry to sort of hash out what are the divisions that are appropriate. I mean, is it appropriate to consider renals as a separate thing; carotids as a separate thing? Subclavians could gain approval provided they have good safety data based on the fact that iliacs, you know, are the same devices, the same sizes. I think we can talk about where you lump and where you split and while today's

issues were focused on the iliac, to me it would seem appropriate and reasonable for the panel, as a group that is supposed to represent the interests of patients and furthering patient care, to take on this issue and wrestle with it in a prospective, forward looking fashion rather than get stuck in a situation where, hey, we can't get these trials done because nobody is enrolling because they have protocol stents, or whatever reason.

DR. WHITE: Let me just say one thing. The other thing about iliacs that I think is critical is that you have lost control -- not you personally, but we have lost control. Every iliac stent going into patients today has not gotten FDA approval in the vessel. It is great for biliaries and I am using it because I think it is true. But I think it is very important we recognize the facts, and the facts are you can say we are going to approve iliacs and we can focus on iliacs but remember that then the iliacs will become the surrogate for every other vessel in the body, which is okay with me because right now the biliary serves as a surrogate for every other vessel in the body. So, I think we are moving ahead if we get to the iliacs. That is good. But remember that we

are talking about the vascular distribution. Ken and I can work out our little differences between how much we lump and split, but the point is that it is very important that we find a way to bring the devices into the vasculature for approval so that we are sort of decriminalizing the clinicians out there who are being now forced to sort of make this end run. The industry is being forced to make that. So, I think it is important that we find workable solutions for doing the trials, and that is what I think this is about.

DR. ROBERTS: Can I just ask a quick question, Dr. White? Why would you even have coronaries separated out --

DR. WHITE: By size.

DR. ROBERTS: Really, if you are going to talk about a vessel as a vessel, you know, they are not very smart these vessels. They all respond kind of the same way.

DR. WHITE: There is a major size differential.

DR. ROBERTS: Well, the tibial vessels are basically the same as the coronaries.

DR. WHITE: Which vessel?

DR. ROBERTS: The tibials.

DR. WHITE: Actually, in the tibials we use coronary stents.

DR. ROBERTS: That is what I am saying.

DR. WHITE: I believe size is the primary discriminator for stent performance.

DR. ROBERTS: I am not trying to be confrontational; I am just trying to figure out how you are defining when you might pick one or another.

DR. WHITE: I think there is no way that we are ever going to be able to solve the lumping and the splitting problem. You know, Solomon is long gone. So, what we have to do is come to a rational way to approach the problem and an acceptable number of exceptions, and certainly naming every vessel for approval is not acceptable. Then, the next step is how much are you willing to lump and split? And, I presented a very extreme view of only two categories. Certainly, we could come up with five. Two is very extreme. I don't think you can do one because I think coronary applications have completely different complications than the peripheral applications. I think the complication and organ kind of things lend themselves better that way but I would be

willing to talk about three or five groups.

DR. TRACY: Can we maybe move along here to the next presenter, please?

DR. STAINKEN: If somebody could put the slides up, I would appreciate it.

[Slide]

This is an important moment. I am from SCVIR and my name is Brian Stainken. ACC and SCVIR appear fundamental to agree. That is a great thing. That said, I would have to say that only a cardiologist could present -- and this is meant gently and humorously -- that the world consists of the heart and then everything else.

[Laughter]

I think that the comments are important and interesting but, clearly, I use coronary stents on a daily basis also all over the body. It is the physical properties of the stent that we are looking to describe as well as, in the splitting category, we want to assess what the alternative procedures are, particularly the surgical procedures and how they fit into the equation. So, I suppose at the end of the day I am a splitter.

[Slide]

As I said, I am representing the Society

for Cardiovascular and Interventional Radiology today. I do have to disclose a few things. First off, I came here from Baltimore, Maryland so I don't think I will even bother to submit a travel claim. I am, however, a consultant with Boston Scientific and the study administration for the All graft trial. In addition, I have participated as a primary investigator in several of the iliac stent trials, including the Corvita iliac, Symphony and Memotherm trial.

[Slide]

We have all discussed the fact that there are only two stents which have conditional approval for the peripheral vascular application. Those are the Palmaz 308, the old balloon-mounted 9-Palmaz stent which I believe is no longer commercially available in its originally approved configuration, and the Yellow Box Iliac Wall stent, which is a miserable stent to use and is not widely used anymore.

[Slide]

Look at the market projections for peripheral stents. You can see that over the next four years the exploding market is going to continue to explode with an anticipated greater

than 200,000 stents placed in America by the year 2004.

Let's look at peripheral vascular approved stents -- almost none and it looks like that number is dwindling further. So what do we do with that big gap between approved stents and application?

[Slide]

First off, why don't we use the Palmaz 308 or the Wall stent? It is because it is obsolete technology at the end of the day. The 308 is no longer available even and the iliac Wall stent shortens dramatically because of its steep right angle. There are problems with wall apposition. In addition, at a practical level, you can't keep Yellow Box Wall stents, Blue Box Wall stents and the other twenty stents that are available in inventory in most departments. It simply costs too much money. Then, there is the issue of introducer size. Most of the newer stents are smaller introducers and, therefore, at least a theoretical benefit in terms of the safety profile.

[Slide]

Why aren't more stents approved? Well, the bottom line in my opinion is that the malignant biliary indication is pretty simple and it is

inexpensive. Second, the absence of approval for vascular indication has no clear marketing or sales impact. It has a huge, as the folks from IntraTherapeutics will tell you, potential financial downside risk but what is the upside for getting peripheral vascular approval right now? Finally, the third issue is that delays to labeling approval create situations where you have obsolete platforms as you are marketing the device and newer stents have already come on the market following a faster pathway than your study device.

[Slide]

So, what are the problems with the iliac stent trials to date? First, the control devices are generally not standard of care. They are obsolete devices. Second, the trial designs in general, in my opinion, have been overly complicated. We have been trying to chase too many data points, resulting in trials that are unworkable. We have had restrictive anatomic criteria, generally by the sponsors, in an attempt to show the device in the best possible light. And, we have had follow-up requirements that are all over the place, including such things as treadmill testing, routine follow-up angiograms

which most of us know patients will not submit to, and duplex scanning for iliac lesions which many of us would agree can be difficult. Third, the eligibility criteria are not the standard of care frequently for these devices, and that is the issue of primary stenting that we have been discussing.

[Slide]

So, why is it that many operators to stent iliac lesions primarily? I think there actually are some reasonable justifications for that. One is that it is a one-step intervention. In general, in most of medicine that is preferable to a multi-step intervention. Why? It is faster. In the real world that means you can turn over your suite quicker. We all know reimbursement is dwindling. We need to keep the volume moving through the suite so we can stay in business. But there are secondary issues that play into speed. Those are radiation dose, contrast dose, patient discomfort, etc., etc.

Second, it is simpler. There is a very heterogeneous group of operators practicing iliac stenting currently. Placing a stent is a fairly simple procedure to do, certainly simpler than doing an angioplasty, assessing the result,

assessing the gradient, re-intervening generally with a larger introducer to place the stent. It is much easier to do the one-step procedure.

Stents are generally much more reproducible than angioplasty. You don't deal with that downside risk factor, the angst of wondering whether your angioplasty worked or not, including late recoil issues.

Next, stenting tends to be reliable. It tends to be dependable. We can all agree that compared to a perfect angioplasty it may not offer a great advantage but pretty much every stent produces a cookie-cutter consistent result. Finally, stenting reduces or possibly even eliminates early stent failure or early intervention failure, if you will.

The next issue is one of perception. That is, many of us perceive that stents are associated with better early term results, although I agree that that is yet to be proven.

[Slide]

What should our objectives be here today? Well, we want to try to facilitate peripheral vascular approval. We want to try and close the gap between approved devices and clinical

application. We all agree that it is a bit ludicrous currently. How do we want to do that? We want to try to modify trial designs and bring them into terms that are more consistent with current data, standard care of practice, and more flexible in attempt to try to accommodate some of the changes in technology which are proceeding at an incredible pace and changes in science. Finally, we would like to adjust trial designs so that we can decrease time to market.

[Slide]

Is there an advantage to randomization? I think we have all agreed, every presenter here, probably not. What about literature or historical controls? Again, those offer all sorts of opportunities for new problems, including the definition of an acceptable historical control, the potential for variable controls for the same class of devices, and the opportunity for skewing your data favorably one way or the other.

[Slide]

So, what about objective performance criteria? In my opinion, those will help to simplify or streamline trials by facilitating enrollment. You can double your enrollment rate off

the top because you eliminate your control arm. Reduce cost to the industry. If we have a consistent trial superstructure and statistical model that would be a huge bonus for industry to work with us in this area. Reduce risk. It would make this practice fair across the board for different manufacturers. It would offer us a consistent, identifiable benchmark with which the industry folks might be able to assess their own prototypes and determine whether it is a marketable device or not. And, it offers the opportunity to be versatile, respond to changes in the marketplace and in our scientific understanding.

[Slide]

The objective performance criteria should be to clearly identify and define variables critical for the safe and effective performance of iliac stent procedures. We should try to quantify the threshold for acceptable performance and follow-up, and we have discussed this already this afternoon.

[Slide]

I would like to propose, if it is acceptable to you, that a SCVIR-FDA device forum might be an appropriate vehicle to develop a

prototype document of this sort.

[Slide]

In conclusion, the development of clearly defined and detailed objective performance criteria for iliac stent procedures will simplify clinical trial design and reduce clinical trial cost and risk to the manufacturer. That is how we get their buy-in. Objective performance criteria will also produce more useful comparative data between stent platforms. Finally, by streamlining the approval process we create an opportunity to realign device indications and applications in the iliac arterial tree. Thank you.

DR. TRACY: Thank you. Are there any other comments anybody wants to make in this part of the open public hearing?

MS. PETERSON: As I was sitting here, listening to everyone, I am not a proponent of repeating things for the sense of doing them and reinventing wheels, and just as food for thought, recently vascular grafts were reclassified to Class II. To Dr. Roberts' point, they are dimensionally based; they are not indication or anatomical location based. So, is there a pattern of another way to get procedures on the market, such as

stents, where we have a vehicle through the agency that we could mimic and maybe really streamline this for everybody?

DR. TRACY: Thank you. Any other comments?

DR. ROSENFIELD: I think Dr. Stainken's presentation -- we agree; you are right. What I would propose is that rather than the SCVIR technology forum that works with the FDA, that a multi-disciplinary group be put together of vascular specialists, including vascular surgeons, radiologists, interventional radiologists and vascular-oriented cardiologists that could serve in an advisory capacity to the FDA in some fashion to help develop OPCs and work with the FDA to propose trial design.

DR. TRACY: One more.

DR. STAINKEN: Just to close and conclude, I would suggest that perhaps the forum that exist and is not working might still be the vehicle; simply invite more people to participate. Thank you.

DR. TRACY: Thank you, everybody, for your comments. We will take a very brief, three and a half minute, break and then we will resume with the

open committee discussion.

[Brief recess]

Open Committee Discussion

DR. TRACY: Could everyone please take their seats? This is the open committee discussion portion of this afternoon's meeting and we will jump directly to the abbreviated questions that the were asked of the panel.

Panel question number one was given our current understanding of stenting in the iliac artery following suboptimal angioplasty, please discuss the need for a randomized control trial to evaluate a new iliac stent system for a suboptimal indication.

I think the thing that has come through to me loud and clear throughout the day is that it is a similar problem that is seen in many other trials for any device really where you are always chasing after technology and, obviously, for this particular indication there are a number of stents that are being used that have not been subjected to comparison with angioplasty or with medical therapy or with surgical therapy and are really being used, I assume, without having an adequate registry to keep the information on the results of using those

stents. So, I think it is probably, at this point, not realistic to think that there could be a randomized control trial to evaluate a new iliac stent system because I am not sure against what it would be randomized. An off-use biliary stent or an adequate stent, surgery, medical therapy? I think it becomes a very difficult question, and I think it is very unfortunate because I am not convinced that the results of stenting are any better than a little medical therapy and stopping smoking, and I just think that we have lost the opportunity to know that at this point in time.

It is really a difficult thing when there is a very obvious desire for the physician to get a good result for their patient and to see that good immediate result and somehow equate that with a long-term result. I don't think it is fair to do that to the patient. It may be getting them out of the lab quickly and safely but it is not guaranteeing that they are going to be walking around in five years on that leg.

So, to take all that into account still, I think it is not possible to have a randomized trial, and I think my opinion would be that developing some type of OPC is probably reasonable.

Given that 90 percent of the creep that I have the sense would be taking place, how would you stop a person from saying, "oh, I failed; let me put in a stent at this point?" It turns out that 90 percent clinically are being done, if not intentionally with that endpoint, that seems to be clinically what is happening. So, the horse is out of the barn at this point in terms of going back to something randomized certainly for a suboptimal result. And, I am very worried about the idea of a randomized controlled trial for a primary iliac dilatation.

I don't know if anybody else can come up with anything more cogent than that, but I think the idea of people putting their heads together to come up with some type of OPC is probably a very good idea.

DR. FREISCHLAG: I did notice that a surgeon didn't talk, and I am not sure if we were asked and denied or not asked, but I want to make sure people know that there are a lot of vascular surgeons that do this intervention. Certainly, if you are going to have this forum to put heads together it has to be all three.

I think the one thing that surgeons may

understand a tad better is the vessels and that we have touched them. Not that that makes us special or better, it is just that when you touch a subclavian and sew to it, it is a whole lot different than an iliac. It is not the same. Even one subclavian to another patient isn't the same. So, I guess I plead that everyone is different. Certainly, for vascular surgeons the indication is so key. The pot is only so big in the next ten years to treat patients with vascular disease. There is no money out there. We all sort of figured that one out.

Therefore, if the pot is so inclusive to treat any lesion you see on an angiogram I think we are going to miss the point of the patients that need the intervention in order to have a better quality of life and in order to benefit from our intervention, no matter which stent we use. When you get a sick patient you may not be able to treat them because the pot is empty come the end of the year. That sounds a little strange but I see it happening in California where there is only so much they are allowing us to do and, certainly, follow-up is a really bad problem in California. They don't let them come back to see you for fear you

might find something wrong and you might do something else. So, I think follow-up is the most key thing here. We learned that this morning, if you are going to decide something is better than something else. I had a patient with two stents that just went down Friday, and she was 18 months out. So, just looking at 30 days or six months, I don't think will answer those questions.

I think it is a great idea to get all the specialists together that want to treat this and to look at the new technology to try to grab a hold of it, and perhaps compare technologies to each other, even though it is not something we have done before. We have tried to avoid that. I think that with good follow-up and good indications it would be great.

Then, one more little rah for surgery, surgery has changed too in the last ten years. We do things and our morbidity and mortality is much lower than it has ever been. Our length of stays for aortas at UCLA is 2.7 days; our carotids are 0.9 days. So, surgery has a different ambiance also that perhaps needs to be put into the equation.

DR. SIMMONS: I appreciate Dr. Zipes'

letter and I do agree that it is a very similar situation to radio frequency oblation and that everybody is doing it. But I think there are differences that have been pointed out here. That is, with radio frequency oblation it was pretty much a black and white issue. Either they had the arrhythmia or they didn't have it, and it was there or it wasn't there and that is why it was so good. But I think this is a little greyer here. I mean, everybody is doing it and they say that this is so much better than whatever is out there but, yet, nobody has ever done the trials to show that it is better than what is out there. The thing is there are other things out there to treat this. I don't know, I think it is a different situation.

Fortunately, having been here a few years, I recognize the FDA doesn't have the power to enforce a randomized trial. They just don't have that power and we have to live in the practical world, and if everyone is going to do it and they are not going to enroll patients in the unattractive clinical alternative, your OPC may be your only alternative.

MR. DILLARD: If I could just make a comment on that, I guess I wouldn't characterize it

as not having the power to force somebody to do a randomized controlled clinical trial. I think we have a little bit different focus, which is trying to focus on the right trial to get the right answers. If the right trial to get the right answers is a randomized, concurrently controlled clinical trial then, in fact, we will ask for that, knowing that we ultimately have to make the decision whether something should be on the market or not.

I think that what has become apparent to all of us, including us at the FDA, is that we need to have a flexible approach to learning in the clinical arena, and once we start understanding about a technology perhaps it is time to take a look at the type of clinical trial that we need to answer subsequent questions either on similar technology or on next generation technology.

So, one of the things that I think we are kind of asking in all these questions, and I don't mean to put Dr. Wittes on the spot here, but perhaps she has some comments, and others, on what do we do as products start becoming standard of care when, in fact, the approval lags for whatever reason, you know, partially pointing the finger at

the FDA but maybe partially at clinical trials and/or how quickly clinical thought evolves. What is it that we can do to try to keep up with that to help design the right trials, and when do we make the decision to change? What are some of the guidelines for that? So, I only pose that not to derail but I think that is really the over-arching piece outcome all of our questions.

DR. WITTES: This is a hard thing for me to answer. I, obviously, feel uncomfortable coming on board on a statement that says just because the train is on the track doesn't mean we don't need to ask the question about efficacy, which seems to me is saying yes to this question. On the other hand, when trains are on the track, you know, it is hard -- obviously you can't do the naive trial again. And, I am just really reiterating what you are saying which is that there are different trials and different designs for different questions, and a blanket statement that from now on a trial is not needed seems wrong to me, even though it is hard to imagine in the abstraction what question would be asked by what trial.

There are registries in other areas where I think a lot of information has been learned, and

maybe this is a place to think about registries and clinical outcomes that make sense with long-term follow-up. In so doing, there may in fact come out to be questions that can be answered, that manufacturers will want answered by a clinical trial. I mean, they may say, my goodness, my device is better in such-and-such an area. It seems to me that the plate needs to be open and there need to be strategies for approval that don't include trials. The situation now sounds like everybody is using the devices anyhow.

But when I hear that we are talking about 300,000 stents of these types to be used in the next few years, it just sounds to me -- I can't really believe that there aren't any rigorous questions to ask of that at least for subsets of the devices and for subsets of questions to be asked. So, that is my comment.

DR. TRACY: I think it is a very difficult situation when you have of those 300,000 procedures being performed and the overwhelming majority are being done off-label. So, to try to enforce any type of registry on that seems difficult, but maybe something voluntary would be appropriate if it is at all possible to institute something like that

because it does not make sense to compare with an antiquated device, which just shows how quickly the technology is moving along. But there will always be people with equally extensive disease who would prefer surgery or who would prefer medical therapy and somehow information needs to be captured on those people because anything that we have seen either presented today or in the referred data has not shown, to me, superiority to plain angioplasty. Certainly, I am not totally convinced that it is superior to medical therapy, nor am I convinced at all that it is superior to surgical therapy. So, we have to remember that, that we don't know these endpoints. We don't know.

DR. NAJARIAN: I just have a question. Is it our job I guess as the FDA to decide whether something is as effective as something else, or if one therapy should be used versus another, or if a given therapy is safe? That, I guess, is the dilemma that I am in.

MR. DILLARD: Let me comment on that because even with the passage of the Food and Drug Administration Modernization Act of 1997, a number of things changed. The one thing that did not change in either the standard of 510(k) or

premarket approval application, either one, was that safety and effectiveness in terms of the language are still in both of those processes. So, under the 510(k) we still have to determine that a product is as safe and as effective as a product that is on the market. And, the PMA standard is still that the product has to be proven to have reasonable assurance of safety and effectiveness.

So, I think pulling effectiveness out of the equation at this point is not only dangerous but something that we can't do. So, I think we still need to have that focus, and it is an important focus, on both of those components when we design our clinical trials.

DR. TRACY: I think what you said is very important, that it doesn't have to necessarily be more effective.

MR. DILLARD: Correct.

DR. TRACY: The other issue in a device such as this is there may be the acute safety but then there is the long-term safety, things that are not defined, captured or even looked at in the short-term trials that I always worry about.

DR. AZIZ: I think, clearly, randomized trials are the way to go, but I think, as we have

seen, there are devices that are already being used. In my mind, it is what is the control group that you are really going to compare it against whether it is a randomized trial or whether it is a retrospective trial. I think the problem that one has to battle with clearly is what are you going to use as a control group.

Even though it is a moving target and new technology may come out tomorrow, I think the safety and efficacy will obviously be demonstrated, but at least in my mind, and probably in the company's mind and also from a lot of the interventionists, the device they produce has to be tested against something, and if you have a randomized trial and you can't have a control group you are really not doing anything. I think probably, by the nature of the way that practice is being done, it has to be compared to something else unless you just say let them use control groups and I think some devices have been passed where they just looked at control groups.

So, I think the train really is moving on, and I think a lot of interventionists are going to be using the devices off-label. It is hard to get things that are good out there quickly without

actually impeding progress. A case in point would be the thoracic aneurism and traumatic aortic tears where surgery is the standard of care. We have done a few cases where we put the endovascular stents off-label and the patients have done really well. These are isolated case reports.

I think we have to grapple with how can we get good things to the patients without actually necessarily focusing too much on the niceties of having a randomized, controlled trial. Is it safe? Is it effective? In many cases some of these things are needed, particularly in the thoracic stent area, which at the moment, from what I see, is really grappling to get those devices out for acute type B dissections, for traumatic aortic tears. I think for some reason we are impeding progress. We know that these patients don't necessarily always benefit well from surgery type B dissections. I can tell you they are very difficult cases to operate on. I think traumatic aortic tears, a lot of the patients we do -- not that you can't sew it in half an hour, but these are guys who have contusions, have head injuries, and I think I would rather some interventionist go in and put a stent in. In fact, I think that would

do the patient good.

So, in my own mind, I personally think that in some of these areas to request or demand a randomized trial may not be the right way to go, and I think there is nothing wrong with that. Although it is scientific purity, I think it won't be a practical necessity.

DR. TRACY: That is a very good comment. The other additional thing is that whatever vehicle is being used to compare, there has to be recognition of what is that vehicle and how are things changing clinically to try to keep current with the thinking in disease management, which means that these registries that we are sort of loosely talking about have to be very structured, and have to be prospectively organized. Part of the trouble we saw today was trying to look at something retrospectively but setting it up prospectively to gain the information that we really need to follow the safety and effectiveness of these devices over time.

DR. AZIZ: I think the focus should be that these gadgets or these devices are not doing any harm. I can tell you just from personal knowledge Chris White and a number of his

colleagues at Ochsner have done some very innovative things. Chris can correct me if I am wrong, cases with patients crescendo and TIAs where the neurosurgeons didn't want to operate on those patients, but I think they took a risk among themselves and put stents in and the patient didn't develop a stroke. I, for one, was fairly impressed when I heard things of that nature.

So, I think we mustn't impede progress for the sake of scientific data collection as, for example, the cases they have done haven't precipitated a stroke. That information should be in the registry.

DR. WITTES: I would like to make a point. I guess I am never convinced by the argument that says something doesn't do any harm. I mean, we want more than that.

MR. DILLARD: Your comments pretty well address number one and two for our questions.

DR. TRACY: Okay. Then, panel question three, stenting in occluded iliac arteries, please discuss the adequacy of a registry trial design, a historic control or objective performance criteria. That is 3a.

3b, please comment on trial endpoints and

the appropriate length of study follow-up for these patients.

Total silence! Since I think we don't have different information to work on for occluded versus highly stenotic, at this point I think that the same types of concerns would be present for either of them. As far as appropriate length of study follow-up for these patients, since their co-morbid conditions also limit their survival, I think there is going to be some natural limit to the amount of time that you can follow these people. But, I think that could be somehow statistically evaluated -- how long these people survive and is it likely that you would run out of benefit from the procedure -- I think that could be a derived number somehow. Any other comments?

DR. FREISCHLAG: There is a registry that has been developed for the endografts through the vascular societies and it has been extremely successful in trailing these patients. Even with the endografts, even though it sounds like that would be a better treatment, it shows that their survival is about the same as open surgery and about 25 percent of those patients die in five years. So, if you can follow five years in these

patients, with the natural history, 60-70 percent of them will be alive but 30-40 percent will not. So, I think we could get some benefit from using that registry. We actually pulled it out for a VA trial we are going to do with endografts to use the same registry. So, there are some of those registries out there to take a look at.

DR. TRACY: Other comments or questions? No? Panel question four, primary stenting in iliac arteries, please discuss the following points regarding trial design for a primary stent indication: randomized trial; control; superiority versus equivalence and endpoints.

I think we have really touched on most of these points already in the discussion of the other diseases. Anybody have any additional point that would deal primarily with primary stenting? Same concerns? Okay.

Panel question number five, primary stenting in iliac arteries, do you have any other recommendations regarding the trial design for a primary stent indication in the iliac artery?

I don't think there is anything in addition to add. It is just that I think we all recognize the difficulty in setting up this study,

but one thing I would like to emphasize is that follow-up is very, very critical for any of these things that we have been talking about.

DR. ROBERTS: One of the things that I guess I would like to recommend perhaps in terms of this is that one thing that could be considered is to really look at this in terms of kind of what matters to the patient, which is primarily patency, and then to, as best as possible, develop very objective ways of looking at this. And, one of the things that I would recommend not doing is using duplex ultrasound of the iliacs as an endpoint. You know, it is very hard to do. It is hard to get accurate data in that kind of case, and it is probably better to use something like a pulse volume recorder. It is probably not ankle-brachial indices; it is probably something like a pulse volume recorder looking at the pressure both before, immediately after and then, in terms of follow-up for whether or not this artery is open and whether or not you still have flow through the iliac system, separating that out from the distal vasculature because, you know, a number of these patients will have distal disease as well as iliac disease and that starts confounding things.

The other thing is that, as we have found today, I think that to the extent that we can, we need to try and find ways around having to bring these patients back for angiography. We need to try, as best we can. I think this is one of the problems that we get into with the various stent trials. It is very expensive to bring a patient back for an angiogram, particularly when the patient feels fine. We heard that today, that it is very difficult to do that. So, I think to the extent that we can, we need to find some sort of surrogate endpoints for angiographic follow-up. I would submit that something like a pulse volume recording would be a very good way to follow that.

DR. TRACY: Any additional comments? Any other questions from the FDA?

MR. DILLARD: Actually, one more if you wouldn't mind taking a couple of minutes, because what I think I am hearing a little bit is maybe partially what we have come to you all with two or three times lately about sort of some generic issues, and I am hearing a lot of the same thing, and I just want to make sure. If I am hearing this similarly, I can sort of factor it in to other sorts of trials and some of the other areas that we

are dealing with, and maybe not have to bring each one of them to you to necessarily put out on the table. But it sounds like we have a movement afoot to move from the old standby, which is the answer is randomized, currently controlled clinical trial under all circumstances unless we can do something that really is going to satisfy the clinical and/or the FDA to be able to really come to, which is the knowledge base is increasing and we can look towards other clinical trial designs. I hear a move a little bit from the panel -- maybe I am not hearing it correctly -- that it is appropriate and we should take a balanced look at clinical trial design, take a look at individual situations, and that sometimes it is going to call for a randomized, concurrently controlled clinical trial but other times perhaps registries under a similar kind of scenario would be appropriate, number one.

Number two, and I think this is the point I just want to kind of turn back on you in terms of a question, which is as these trials perhaps come to fruition with either newer devices, number one, or some fairly major second or third generation devices that we may be bringing back to you for a recommendation, that there is going to be sort of

an overall acceptance for other than just randomized, concurrently controlled clinical trial designs in order to be factored into decision-making processes. I just want to sort of put that out, not for a lot of discussion, but that is kind of some of the carry-home for me, to say that there is going to be a willingness on your part also to not only work with us on trial design but perhaps have broad basic acceptance of other than randomized, concurrently controlled clinical trial designs.

DR. TRACY: I think I probably speak for the group in saying that if the data that is brought to us is convincing and is something that we can analyze and get an idea is this thing safe; is this thing effective, then that is what we need to have. When we are presented with data that is somehow incomplete, or there is so much missing, or this trial design was so complicated it couldn't be accomplished, even if it theoretically was the purest design it becomes much more difficult to deal with. So, I think you would have our cooperation in accepting other than randomized, controlled trials if that were the appropriate design.

MR. DILLARD: Great.

DR. WITTES: But let me add that very often people think these other designs are easy. They are actually extremely difficult because you don't have the protection of the randomized. So, if you do these kinds of studies, they have to be absolutely meticulous so that you can, in fact, make comparisons that you need to make. Otherwise, the data become uninterpretable.

DR. LASKEY: It is the old story, "what's the question?" I think you really need to go back and that is where it all starts and ends. If you have a good question and it is appropriately pointed, you can usually design a study or hopefully you can to answer that. If the question is fuzzy, then you get into trouble.

That is why I think it is important to distinguish the utility of registry and an observational series from the RCTs. I think it really is very much a question of what you want to find out. So, it is easy enough to look at a consecutive series of acute and threatened closure in a registry and compare that to some database of thousands of cases of iliac stenting. That you can do. But if you are looking for a decided advantage

for treatment A versus treatment B in a disease which has a number of other confounding variables, unless you do the perfect registry, which I am not aware of, you are going to have confounding and you will wind up with all sorts of issues. In that instance, when you are looking for long-term follow-up, perhaps the RTC is the best way to go but, again, it is the question. What is the question? If it has a finite variable as an endpoint you are in good shape but if it is a mess, a composite endpoint of soft and hard variables, and that is often what we deal with -- we deal with that in the stent arena and it is not going to be any different in the peripheral intervention arena.

DR. ROBERTS: I don't know how you do this, but I think it is quite clear that if you can do a good randomized, controlled trial that obviously you get a lot more information and you feel much more comfortable with what the answers are. It almost is that there needs to be an incentive for doing that. In other words, it buys you something. I don't know what the answer to that would be, but it is almost as if somehow you get extra points, or it makes it easier, or something happens because you really do take the

time to do that kind of trial. Granted, when you do that kind of trial it should buy you something because it should be cleaner data. But it is almost like we need to think of a way to incentivize that.

MR. DILLARD: I might just make one comment on that point, and then I will be quiet and make one final comment. In the past many of the randomized, controlled trials that have come out to be successful, and let me just take one particular situation, the superiority trial, many times that does buy them something by way of a claim, whereas if we have a non-randomized, controlled trial, even though it is designed to be a superiority study, many times it does not end up in the types of claims that you would otherwise get from a randomized, controlled trial. So, actually in terms of FDA incentive, there has been some, albeit I won't say generically across the board. So, there are cases where it has ended up in a better claim, which I think we have heard from companies helps them in terms of marketability of their product in many cases. In many cases to you all was the users, having a randomized, controlled trial versus a competitor sometimes helps you make

a decision about which product to buy. So, that has been the incentive that we have heard.

I will just make one final comment, number one, just to thank all of you. I think we are kind of winding down here and I want to thank you all for your effort today, number one, and number two, for letting FDA take the time to make sure that we, at least from a process standpoint, we are trying to do the best job that we could and so I apologize and I thank everybody both in the audience and the panel for bearing with us as we clarified some of that, and we will try to do a better job next time.

DR. TRACY: All right, we will adjourn the open session. Thank you, everybody.

[Whereupon, at 5:05 p.m. the proceedings were adjourned]

CERTIFICATE

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO

CERTIFICATE

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO